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2017-09-28

Sammallahti , S , Kajantie , E , Matinolli , H-M , Pyhälä , R , Lahti , J , Heinonen , K , Lahti , M , Pesonen , A-K , Eriksson , J G , Hovi , P , Järvenpää , A-L , Andersson , S & Raikkonen , K 2017 , ' Nutrition after preterm birth and adult neurocognitive outcomes ' , PLoS One , vol. 12 , no. 9 , 0185632 . <https://doi.org/10.1371/journal.pone.0185632>

<http://hdl.handle.net/10138/227949>

<https://doi.org/10.1371/journal.pone.0185632>

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RESEARCH ARTICLE

Nutrition after preterm birth and adult neurocognitive outcomes

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OPEN ACCESS

Citation: Sammallahhti S, Kajantie E, Matinolli H-M, Pyhälä R, Lahti J, Heinonen K, et al. (2017) Nutrition after preterm birth and adult neurocognitive outcomes. PLoS ONE 12(9): e0185632. <https://doi.org/10.1371/journal.pone.0185632>

Editor: Umberto Simeoni, Centre Hospitalier Universitaire Vaudois, FRANCE

Received: May 11, 2017

Accepted: September 15, 2017

Published: September 28, 2017

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Data Availability Statement: The authors confirm that some access restrictions apply to the data underlying the findings. The Helsinki Study of Very Low Birth Weight Adults data contain sensitive and potentially identifying patient information, even after social security numbers and names have been removed from the data set. The use and sharing of such data are strictly controlled by several clauses of the Finnish law, designed to ensure the protection of privacy. The researchers interested in using the data must obtain approval from the Steering Committee of the Helsinki Study of Very

Abstract

Background

Preterm birth (<37 gestational weeks) poses a risk of poorer neurocognitive functioning. Faster growth after preterm birth predicts better cognitive abilities and can be promoted through adequate nutrition, but it remains unknown whether variations in nutrient intakes translate into long-term benefits for neurodevelopment.

Methods

In 86 participants of the Helsinki Study of Very Low Birth Weight Adults (birthweight <1500g), we examined if higher intakes of energy, macronutrients, and human milk during the first nine weeks after preterm birth predict performance in tests of cognitive ability at 25.1 years of age (SD = 2.1).

Results

10 kcal/kg/day higher total energy intake at 3 to 6 weeks of age was associated with 0.21 SD higher adult IQ (95% Confidence Interval [CI] 0.07–0.35). Higher carbohydrate and fat intake at 3–6 weeks, and higher energy intake from human milk at 3–6 and at 6–9 weeks were also associated with higher adult IQ: these effect sizes ranged from 0.09 SD (95% CI 0.01–0.18) to 0.34 SD (0.14–0.54) higher IQ, per one gram/kg/day more carbohydrate and fat, and per 10 kcal/kg/day more energy from human milk. Adjustment for neonatal complications attenuated the associations: intraventricular hemorrhage, in particular, was associated with both poorer nutrition and poorer IQ.

Low Birth Weight Adults. The Steering Committee is accountable to the national register authority (the Finnish National Institute for Health and Welfare) and to the ethics committee which has approved the study protocol (the Ethics Committee for Children and Adolescents' Diseases and Psychiatry at Helsinki University Central Hospital, Finland). To request the data, we recommend first contacting Dr Eero Kajantie (eero.kajantie@thl.fi). The Registry Office of the Finnish National Institute for Health and Welfare can be contacted at kirjaamo@thl.fi.

Funding: This study was part of the Helsinki Study of Very Low Birth Weight Adults funded by the Academy of Finland (<http://www.aka.fi/>), University of Helsinki Research Foundation (<https://www.helsinki.fi/en/university/university-of-helsinki-research-foundation>), the Finnish Medical Society Duodecim (<http://www.duodecim.fi/english/>), Finska Läkaresällskapet (<http://www.fl.s.fi/>), the Foundation for Pediatric Research in Finland (<http://www.lastentautientutkimussaatio.fi/>), the Finnish Special Governmental Subsidy for Health Sciences, the Jalmari and Rauha Ahokas Foundation (<http://www.ahokkaansaatio.org/>), the Juho Vainio Foundation (<http://www.juhovainionsaatio.fi/>), the Emil Aaltonen Foundation (<http://www.emilaaltonen.fi/>), the Novo Nordisk Foundation (<http://www.novonordisk.com/about-novo-nordisk/corporate-governance/foundation.html>), the Päivikki and Sakari Sohlberg Foundation (<http://www.pss-saatio.fi/>), the Signe and Ane Gyllenberg Foundation (<http://gyllenbergs.fi/>), the Yrjö Jahnsson Foundation (<http://www.yjs.fi/>), the Orion-Pharma Foundation (<http://www.orion.fi/tutkimus/orionin-tutkimussaatio/>), the Sigrid Jusélius Foundation (<http://sigridjuselius.fi/>), the Finnish National Graduate School of Clinical Investigation (<http://www.vtkk.fi/>), Hope and Optimism Initiative (<http://hopeoptimism.com/>), the Wilhelm and Else Stockmann Foundation, and the Pediatric Graduate School, University of Helsinki (<http://www.kll.helsinki.fi/tutkimus/lnktko.html>). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Conclusion

In preterm neonates with very low birth weight, higher energy and human milk intake predict better neurocognitive abilities in adulthood. To understand the determinants of these infants' neurocognitive outcome, it seems important to take into account the role of postnatal nutrition, not just as an isolated exposure, but as a potential mediator between neonatal illness and long-term neurodevelopment.

Introduction

Preterm birth (before 37 gestational weeks) poses a risk of poorer neurocognitive functioning. This risk is highest for those born very preterm (<32 weeks) or at very low birth weight (VLBW; <1500g), and effects span beyond childhood. [1–4] Explaining this vulnerability are factors that underlie and result from preterm birth, including pregnancy complications and immaturity-related health problems. All these factors can reflect on slow neonatal growth, which predicts poorer adult neurocognitive outcome. [5,6] However, it remains unknown whether variations in nutrient intakes after preterm birth not only accelerate growth, but also translate into long-term benefits for neurodevelopment.

In preterm children, higher neonatal energy intake predicts better neurodevelopment, but neonatal illness may underlie this association. [7] We know of only a handful of studies that have examined nutrition after preterm birth in relation to neurodevelopmental outcomes beyond childhood, and these studies have not specifically addressed the issue of neonatal complications potentially influencing both nutrition and neurodevelopment. One set of studies included preterm individuals with birth weight <1850g, who were originally recruited into two separate randomized feeding trials and whose data were later combined. Within this population, those who received multinutrient-enriched preterm formula, versus non-fortified donor milk or standard formula, had higher verbal intelligence quotient (VIQ) at 13–20 years of age. [8,9] In a subset of the same population, those who received more maternal milk had higher VIQ at 13–20 years. [10] Contrastingly, another study of small-for-gestational-age VLBW adults found no association between neonatal energy intake and general intelligence at 23 years of age. [11]

In our cohort of adults born preterm at VLBW, we examined whether intakes of energy, carbohydrates, protein, fats, and human milk during the first nine weeks of life predict general intelligence, memory, attention, and executive functioning at 25 years of age, when taking into account important pregnancy-related and neonatal factors.

Methods

Participants

The *Helsinki Study of Very Low Birth Weight Adults* has been previously described. [12,3] We invited the 255 individuals born between 1978 and 1985 with VLBW who were discharged from the neonatal intensive care unit of Children's Hospital at Helsinki University Central Hospital, Finland, the only such unit in the Uusimaa province, and who lived in the greater Helsinki area as adults, to participate in the first clinical visit in 2004–2005: 166 participated. In 2007–2008, 159 of these 166 individuals could be traced and invited to a second visit, which included neurocognitive testing: 113 participated. [3,6,13–15] We excluded participants with blindness (n = 2), cerebral palsy (n = 6), or intellectual developmental disability (n = 1), and

those for whom sufficient nutrition data were not available ($n = 18$), resulting in an analytic sample of 86 participants (mean gestational age 29 weeks, standard deviation [SD] = 16 days, range 24–35 completed weeks; mean birth weight 1116g, SD = 219g, range 600–1480g; mean age at follow-up 25.1 years, SD = 2.1 years, range 21.6–29.7 years). All participants gave written informed consent, and the Ethics Committee for Children and Adolescents' Diseases and Psychiatry at Helsinki University Central Hospital approved the study protocol.

Selective attrition

We compared the analytic sample ($n = 86$) with those who could not be included because of non-participation or missing data ("drop-outs", $n = 145$), and found no differences in gestational age, sex, birth weight standard deviation score (SDS), parental education, maternal smoking during pregnancy, preeclampsia, neonatal complications, nutrition in infancy, age at follow-up, or neurocognitive outcomes (p -values > 0.05). We excluded all those with blindness ($n = 2$), cerebral palsy ($n = 16$), or intellectual developmental disability ($n = 6$) from these comparisons. The number of drop-outs whom we could include in each of the comparisons varied (gestational age, sex, birth weight, and preeclampsia data were available for all 145 drop-outs, maternal smoking data for 137 drop-outs, parental education for 80 drop-outs, neonatal complication data for 105–145 drop-outs, nutritional data for 37–53 drop-outs, age at follow-up for 18 drop-outs, and neurocognitive data for 16–17 drop-outs).

Nutrition

Nutritional data during the initial hospital stay came from hospital records and was available for the first 9 weeks of life (after which the number of participants with sufficient data was reduced because of hospital discharge). As previously described in more detail, [16] we divided the data into 3-week periods (birth to 3, 3–6, and 6–9 weeks of age), and calculated daily mean *total energy intakes* and *energy intakes from protein, fat, and carbohydrates* from all enteral and parenteral nutrition, and *energy intake from human milk*, including donated and mother's own milk, per kilogram bodyweight. The macronutrient content of the mother's own milk was estimated based on the nutritional composition data published by Anderson et al. [17], who followed the milk content of mothers who delivered preterm. The nutritional composition of banked human donor milk was based on values published by Rönnholm et al. [18,19], who analyzed the macronutrient content of the banked milk used in the hospital where the infants of the present study were treated.

Enteral feeding was initiated through a nasogastric tube with human milk on 1st–2nd day of life. Milk intake was increased to a maximum of 200ml/kg/day according to individual tolerance, and maintained at this level until discharge. All milk was pasteurized. During the 9-week period, 59 participants (69%) received mother's own milk, 81 (94%) received pooled donor milk, and 19 (22%) received formula. If targeted enteral feeding was not possible, intravenous fluids with glucose were initiated, and amino acids and lipids were gradually introduced from the 2nd–3rd day.

Neurocognitive outcomes

We used four subtests of the Wechsler Adult Intelligence Scale-III [20] (Vocabulary, Digit span, Similarities, Block design) to estimate *full-scale, verbal, and performance intelligence quotient* (IQ, VIQ, and PIQ, respectively). As measures of executive functioning, attention, and visual memory, we used Phonetic (words beginning with letters S and P) and Categorical (animal, vegetable/fruit names) Verbal Fluency [21], the Rey-Osterrieth Complex Figure Test [22], the Trail Making Test [23], the Bohnen version of the Stroop Test [24], and the Conners'

Continuous Performance Test [25]. Indices of these latter five tests correlate highly, and we thus used principal components analysis with Varimax rotation for data reduction. The first four components with eigenvalues >1 explained 75% of the total variation [6] and were named *Verbal flexibility* (higher scores reflected better Fluency and Stroop scores), *Visual flexibility* (better Trail Making Test scores), *Visual memory* (better Rey-Osterrieth Complex Figure test scores), and *Impulsivity* (faster Conners' Continuous Performance Test reaction times and more commission errors) (S1 Table).

Confounders

From medical and birth records, we collected *sex*, date of birth for calculating *age at adulthood follow-up*, self-reported *maternal smoking during pregnancy* (no/yes), *preeclampsia* (no/yes, diagnosed using standard criteria [26]) *gestational age* based on last menstrual period and confirmed by a neonatologist (ALJ), and birth weight for calculating *birth weight SDS* according to Finnish standards. [27] During the adulthood follow-up, participants reported the *highest education of either parent* (basic/secondary/lower tertiary/upper tertiary), as proxy of parental neurocognitive abilities and socio-economic status. As *neonatal complications*, collected from medical records, we included *septicemia* (no/yes, diagnosed if infant showed symptoms and a blood culture was positive), *bronchopulmonary dysplasia* (no/yes, diagnosed by a neonatologist [ALJ] based on Northway criteria [28]), *patent ductus arteriosus* treated with indomethacin (no/yes, including those who also underwent corrective surgery), *blood exchange transfusion* due to hyperbilirubinemia (no/yes), duration of *ventilator treatment* (no/0-7/8-14/15-28/>28 days), and *intraventricular hemorrhage* (IVH) (no/grade I-II/grade III-IV). No participant was diagnosed with necrotizing enterocolitis. Neonatal cerebral ultrasound was being introduced during the study period, [29] and despite limited equipment and personnel, only 22 participants lacked data on IVH. Four participants lacked data on maternal smoking during pregnancy. These were dummy-coded into separate groups. Two participants who lacked all neonatal complication data were excluded in the analyses which adjusted for these complications.

Statistical analysis

We used linear regression models to test, first, if total energy intake and energy intake from human milk from birth to 3, 3 to 6, and 6 to 9 weeks of age predicted IQ, PIQ, VIQ, Verbal flexibility, Visual flexibility, Visual memory, and Impulsivity. Moreover, we tested associations between protein, fat and carbohydrate intake (g/kg/day) during the same three-week periods, and IQ. We square-transformed IQ and PIQ to improve linear model fitting, and standardized the outcomes within the sample (mean = 0, SD = 1) to facilitate comparison of effect sizes.

In Model I, we adjusted for gestational age, sex, birth weight SDS, and age at follow-up. In Model II, we adjusted for Model I factors, parental education, maternal smoking during pregnancy, and preeclampsia. In Model III, we adjusted for Model I factors and the neonatal complications described above. We also tested if associations varied by sex or by birth weight SDS, by including a product term ('sex x nutrition' or 'birth weight SDS x nutrition') into the regression equation accompanied by main effects and other Model I covariates. Further, we tested whether total energy intakes, energy intakes from human milk, and IQ differed between those with versus those without each neonatal complication, and whether IQ differed between those who received mother's own milk versus those who did not: we used analysis of variance for duration of ventilation treatment and t-tests for dichotomized complications and for feeding with mother's own milk. We used IBM SPSS Statistics 24 for statistical analyses and considered two-tailed p-values < 0.05 statistically significant.

Results

Characteristics, nutritional intakes in infancy, and neurocognitive test scores in adulthood are presented in [Table 1](#).

General intelligence, total energy intake, and energy intake from human milk

[Fig 1](#) presents associations between total energy intake from birth to 3, 3–6, and 6–9 weeks and general intelligence: Those with higher total energy intake from birth to 3 weeks had higher PIQ (0.16 SD per 10kcal/kg/day), and those with higher total energy intake at 3–6 weeks had higher IQ, VIQ, and PIQ (0.16–0.21 SD per 10kcal/kg/day) (Model I). [Fig 2](#) presents associations between energy intake from human milk and general intelligence: Those who received more energy from human milk from birth to 3 weeks had higher PIQ (0.13 SD per 10kcal/kg/day), those with higher milk intake at 3–6 weeks had higher IQ and PIQ (0.16–0.19 SD per 10kcal/kg/day), and those with higher milk intake at 6–9 weeks had higher IQ and VIQ (0.09–0.10 SD per 10kcal/kg/day) (Model I).

Associations remained similar after further adjustment for parental education, maternal smoking during pregnancy, and preeclampsia (Model II), but adjustment for neonatal complications attenuated them, rendering them non-significant (Model III) ([Figs 1 and 2](#)).

General intelligence and carbohydrate, protein, and fat intakes, and the intake of mother's own milk

Higher carbohydrate intakes at 3–6 weeks were associated with higher IQ and VIQ; higher protein intakes from birth to 3 weeks with higher PIQ, and higher fat intakes between birth and 6 weeks with higher IQ, VIQ and PIQ in Model I (effect sizes 0.18–0.73 SD, per gram/kg/day of carbohydrates/protein/fat) ([S2 Table](#)). Only the associations between fat intakes at 3–6 weeks and IQ and VIQ survived adjustment for neonatal complications (Model III, effect size 0.26 for both IQ and VIQ, p -values < 0.05).

In an additional analysis, we compared those who received mother's own milk ($n = 59$) against those who did not ($n = 27$): no statistically significant differences in IQ, VIQ, or PIQ between the two groups were observed ($p > 0.07$).

Attention, memory and executive functioning, total energy intake, and energy intake from human milk

Better Visual memory was predicted by higher total energy intake from birth to 3 weeks (effect size 0.19 SD per 10kcal/kg/day more energy, 95% CI 0.05–0.32 in Model I, p -value = 0.02 in Models II and III) and at 3–6 weeks (effect 0.22 SD; 95% CI 0.06–0.38 in Model I, p -values = 0.01 and 0.35 in Models II and III, respectively), and higher energy intake from human milk from birth to 3 weeks (effect 0.11 SD per 10kcal/kg/day more energy from human milk, 95% CI 0.01–0.21 in Model I, p -values = 0.06 and 0.08 in Models II and III, respectively). We found no other statistically significant associations between total energy intake or energy intake from human milk, and Visual memory, Verbal or Visual flexibility, or Impulsivity (p -values > 0.11, Model I).

Differences according to neonatal complications, sex, and birth weight SDS

As most associations attenuated after adjustment for neonatal complications, we specified their effects by testing associations between neonatal complications, nutrient intakes, and IQ.

Table 1. Background characteristics, nutritional intakes in infancy, and adult IQ, VIQ, and PIQ among very low birth weight (<1500g) adults.

<i>Characteristic</i>	<i>M (SD)</i>	<i>n (%)</i>	<i>Participants</i>
Background characteristics			
Gestational age, weeks	29.0 (2.2)		86
Gestational age <32 weeks		80 (93)	86
Gestational age <28 weeks		25 (29)	86
Sex, male		37 (43)	86
Birth weight, g	1116 (219)		86
Birth weight, SD score	-1.2 (1.5)		86
Birth weight \leq -2 SD		27 (31)	86
Birth weight <1000 grams		26 (30)	86
Birth length, cm	37 (2.4)		85
Birth head circumference, cm	26 (2.0)		83
Mother smoked during pregnancy		16 (20)	82
Preeclampsia		17 (20)	86 ^a
Age at clinical follow-up visit, years	25.1 (2.1)		86
Highest education of a parent			86
basic/primary or less		8 (9)	
upper secondary		16 (19)	
lower tertiary		35 (41)	
upper tertiary		27 (31)	
Neonatal complications and illnesses^b			
Duration of ventilator treatment, median days (25 th to 75 th percentile / range)	6 (0–21 / 0–80)		84
Septicemia		8 (10)	84
Bronchopulmonary dysplasia		22 (26)	84
Patent ductus arteriosus treated with indomethacin		29 (35)	84
Blood exchange transfusion		14 (17)	84
Intraventricular hemorrhage			64
none		50 (78)	
grade I or II		10 (16)	
grade III or IV		4 (6)	
Mean nutrient intakes in infancy			
Birth to three weeks of age			
Energy, kcal/kg/day	94 (17)		86
Energy from human milk, kcal/kg/day	77 (24)		83
Carbohydrates, g/kg/day	11 (1.4)		86
Protein, g/kg/day	1.4 (0.4)		86
Fats, g/kg/day	4.3 (1.2)		86
Three to six weeks of age			
Energy, kcal/kg/day	119 (15)		82
Energy from human milk, kcal/kg/day	108 (22)		78
Carbohydrates, g/kg/day	12 (1.3)		82
Protein, g/kg/day	1.9 (0.4)		82
Fats, g/kg/day	5.9 (1.0)		82
Six to nine weeks of age			
Energy, kcal/kg/day	125 (15)		79
Energy from human milk, kcal/kg/day	108 (26)		75
Carbohydrates, g/kg/day	13 (1.4)		79
Protein, g/kg/day	2.1 (0.5)		79

(Continued)

Table 1. (Continued)

Characteristic	M (SD)	n (%)	Participants
Fats, g/kg/day	6.2 (1.0)		79
Estimated general intelligence scores			
IQ, standardized score	102 (16)		86
VIQ, standardized score	104 (14)		86
PIQ, standardized score	99 (20)		86

^a We compared mothers among whom we had confirmed diagnosis of preeclampsia to mothers with no indication of preeclampsia in hospital or maternity clinic records.

^b 84 participants had data available on the duration of ventilation treatment, septicemia, bronchopulmonary dysplasia, patent ductus arteriosus for which indomethacin was given, and blood exchange transfusion, and were thus included in the analyses where we adjusted for neonatal complications.

Abbreviations: g: gram; IQ: full-scale intelligence quotient; kcal: kilocalorie; M: mean; n: number of participants in described category; Participants: number of participants for whom data were available; PIQ: performance intelligence quotient; SD: standard deviation; VIQ: verbal intelligence quotient

<https://doi.org/10.1371/journal.pone.0185632.t001>

Those with IVH had lower total energy intake, lower energy intake from human milk, and lower IQ (p-values<0.04) (S3 Table). Those with longer ventilator treatment, bronchopulmonary dysplasia, and patent ductus arteriosus also had lower total energy intake and lower energy intake from human milk (p-values<0.03); although mean IQ's were slightly lower in those with these complications, compared with those without the complications, the differences were not statistically significant (p-values>0.12).

Associations between total energy/human milk/carbohydrate/protein/fat intakes and IQ did not vary according to birth weight SDS or to sex (p-values>0.06 for interactions).

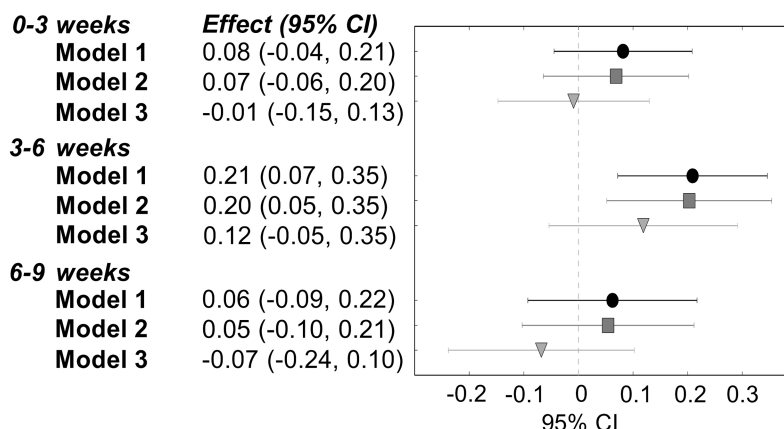
Discussion

In this well-characterized cohort of 86 VLBW individuals, we show that higher energy and human milk intakes during the initial hospital stay were associated with better cognitive functioning in adulthood. The effect sizes of these associations are quite consistent with earlier reports of childhood outcomes [30]: 10 kcal/kg/day higher total energy intake at 3 to 6 weeks was associated with approximately 3 point higher IQ at 25 years of age (equivalent of 0.21 SD). As compared with this period of 3 to 6 weeks, associations between nutrition from birth to 3 weeks or from 6 to 9 weeks and adult IQ were similar in direction, but smaller in effect size. The association between energy intake at 3 to 6 weeks and neurocognitive outcomes appeared to be due to energy from human milk, carbohydrates, and fat. By contrast, protein intake slightly earlier, from birth to 3 weeks, seemed to predict neurodevelopment, particularly non-verbal performance. Overall, early nutrition predicted outcomes ranging from verbal and visuospatial functioning to memory, but it did not predict executive functioning scores.

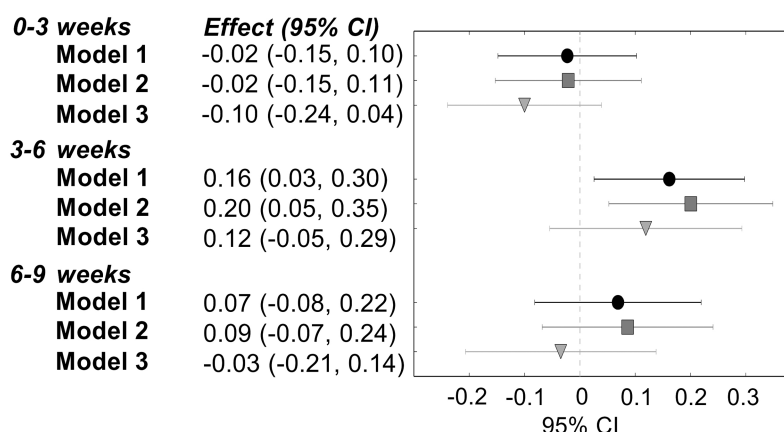
The associations we found between energy, human milk, carbohydrate, protein, and fat intakes and neurodevelopment were independent of sex, gestational age, intrauterine growth, maternal smoking, preeclampsia, and parental socio-economic status. Neither were they explained by manifest developmental disability nor neurosensory impairment.

Interestingly, when a range of neonatal complications were taken into account, no independent associations between nutrition and adult IQ remained, as demonstrated by the reduced effect sizes. IVH, which seemed to be the main down-driver of the effect sizes, was associated with both lower nutritional intakes and poorer IQ. These findings may suggest that nutritional differences reflected, or possibly mediated, the severity of neonatal illness and its effect on neurodevelopment.

A. Full-scale intelligence quotient



B. Verbal intelligence quotient



C. Performance intelligence quotient

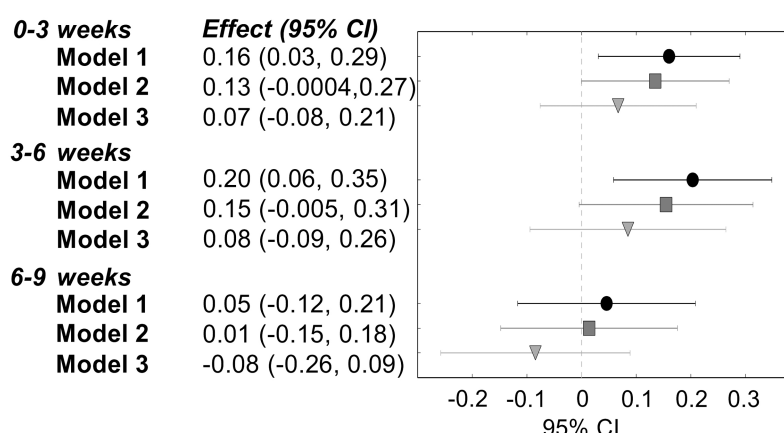


Fig 1. Total energy intake from birth to 3 weeks, 3 to 6 weeks, and 6 to 9 weeks of age, and full-scale, verbal and performance intelligence quotient in young adulthood, among individuals born with very low birth weight (<1500 grams).^a Model I: adjusted for gestational age, sex, birth weight standard deviation score, and age at follow-up. Model II: adjusted for Model I factors, parental education, maternal smoking during pregnancy, and preeclampsia. Model III: adjusted for Model I factors and neonatal complications,

including septicemia, bronchopulmonary dysplasia, patent ductus arteriosus, blood exchange transfusion, duration of ventilator treatment, and intraventricular hemorrhage. ^a The number of participants in each analysis varied according to data availability. At 0–3 weeks, 86 participants; at 3–6 weeks, 82 participants; and at 6–9 weeks, 79 participants had data available on total energy intake and were included in the analyses (Model 1–2). In Model 3, we had to further exclude two people because of missing data on neonatal complications. Abbreviations: CI: confidence interval; Effect: change in full-scale, verbal, and performance intelligence quotient scores, in SD units, for each 10kcal/kg/day increase in total energy intake.

<https://doi.org/10.1371/journal.pone.0185632.g001>

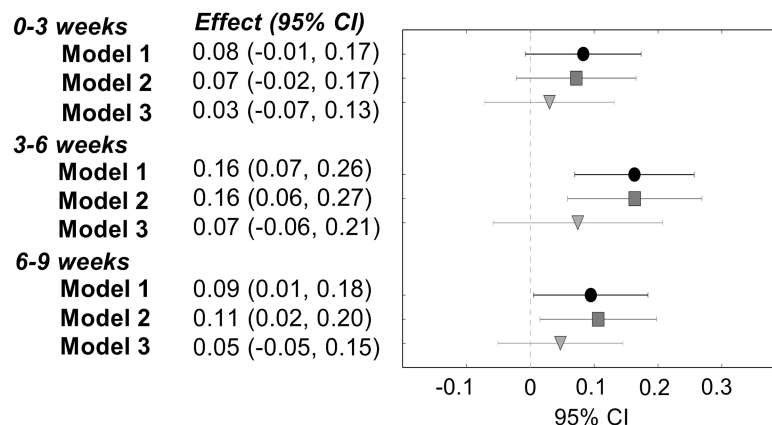
Our adult findings are in line with previous observational studies in ELBW [7,30] / VLBW [31] children, which have demonstrated that higher energy, [7,30] protein, [30] and lipid [31] intakes during the first weeks of life predict better neurodevelopmental scores at 12–22 months, but these effects are driven by the most critically ill neonates. [7] Also in line with our results, randomized controlled studies and meta-analyses have failed to show that multinutrient-enriched, [32,33] protein/amino acid enriched [34–36] or long-chain poly-unsaturated fatty acid-enriched [37,38] (enteral [32–38] / parenteral [33,35,36]) nutrition during initial hospitalization after preterm birth would improve neurodevelopmental scores at or before 12 months, [33,34,37] between 18–24 months, [32,34–37] or in school-age. [34,35,38]

The most compelling evidence exists for breast milk, which predicts better neurodevelopmental outcomes in preterm children at 2–11 years [39–43]—effects that seem less evident at 9–20 months [44,45] and may be diminished when adjusting for maternal intelligence. [46] In our population, who routinely received human milk, neonatal complications seemed to largely explain the association between better neurodevelopment and higher milk intake during the first nine weeks of life, and we did not find differences in IQ between the majority of participants who received mother's own milk during the initial hospitalization and the minority who did not. However, the benefits of breastfeeding were beyond the scope of this study and any far-reaching conclusions concerning the use of mother's own milk based on these data would be ill-advised.

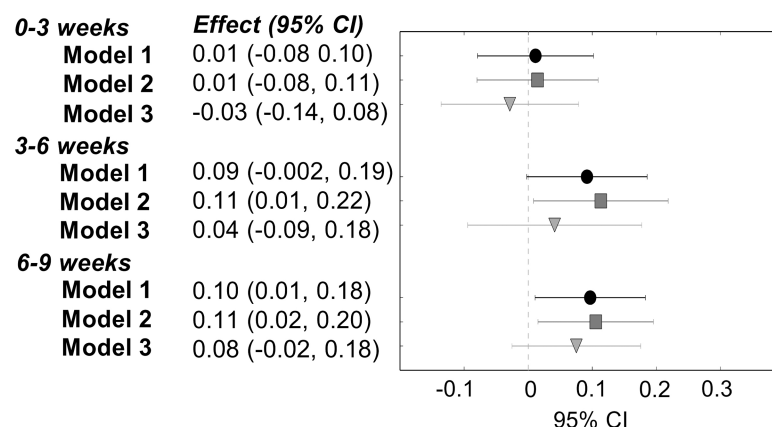
We are aware of only a handful of studies on nutrition after preterm birth which have spanned beyond childhood. In agreement with our results, energy intake during the first 10 days of life was not associated with IQ at 23 years in 46 small-for-gestational-age individuals born with VLBW in 1967–1975. [11] In that study, neonatal complications were not addressed—however, the VLBW newborns' survival rate of 39% at the time suggests that only the healthiest cohort members could be followed-up. [11] In another set of studies, in preterm individuals with birth weight <1850g, those randomized to receive multinutrient-enriched formula (vs. term-formula or donor milk) [8,9] and those who non-randomly received more maternal milk [10] had higher VIQ at 13–20 years of age. The positive effects contrast with the findings in younger children: even within that same population, fortified formula did not consistently improve neurodevelopmental scores at previous follow-ups at 18 months [47] and 7.5–8 years [48]. While it could be that some effects of early nutrition only become apparent with age, attrition complicates interpretation of the findings: of the total of 926 participants who were originally enrolled in those trials, data for only 95 [8], 76 [9], and 50 [10] participants were available at 13–20 years. Further, data on neonatal complications were not available, making it thus difficult to determine the extent to which our findings agree with those results.

Our study strengths include the long follow-up of VLBW individuals to adulthood, validated and extensive outcome data, and detailed pre- and postnatal data. The neonatal nutrition data recorded by medical staff is exceptional for such a long follow-up. In an era when neonatal cerebral ultrasound was just being introduced, 64 of our 86 study participants underwent the scan: a strength for an adult follow-up, yet a limitation in comparison to modern-day cohorts where cerebral ultrasound has widely become routine practice.

A. Full-scale intelligence quotient



B. Verbal intelligence quotient



C. Performance intelligence quotient

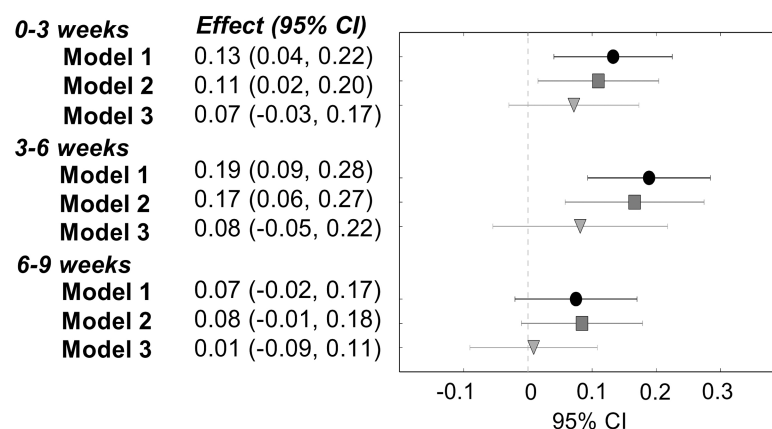


Fig 2. Energy intake from human milk from birth to 3 weeks, 3 to 6 weeks, and 6 to 9 weeks of age, and full-scale, verbal and performance intelligence quotient in young adulthood, among individuals born with very low birth weight (<1500 grams).^a Model I: adjusted for gestational age, sex, birth weight standard deviation score, and age at follow-up. Model II: adjusted for Model I factors, parental education, maternal smoking during pregnancy, and preeclampsia. Model III: adjusted for Model I factors and neonatal complications, including septicemia, bronchopulmonary dysplasia, patent ductus arteriosus, blood exchange

transfusion, duration of ventilator treatment, and intraventricular hemorrhage.^a The number of participants in each analysis varied according to data availability. At 0–3 weeks, 83 participants; at 3–6 weeks, 78 participants; and at 6–9 weeks, 75 participants had data available on human milk intake and were included in the analyses (Model 1–2). In Model 3, we had to further exclude two people because of missing data on neonatal complications. Abbreviations: CI: confidence interval; Effect: change in full-scale, verbal, and performance intelligence quotient scores, in SD units, for each 10kcal/kg/day increase in energy intake from human milk.

<https://doi.org/10.1371/journal.pone.0185632.g002>

Our main study limitation is attrition: 113 VLBW individuals participated in the clinical visit (71% of those invited), and after excluding those with neurosensory impairments and missing nutritional data, we had an analytic sample of 86 individuals. Although those whom we could not include because of missing data did not differ from the analytic sample, loss of follow-up may cause selection bias and impact the generalizability of the results, especially into less healthy groups. We have refrained from post-hoc power calculations, [49] but note that the relatively small number of participants may hinder the detection of small-scale effects, and did not permit us to study subgroup-specific effects, such as potential mediating effects of nutrition within the most severely ill of the VLBW individuals. Neither could we examine how the timing of neonatal complications affected the outcomes, or compare the use of mother's own milk specifically against donor milk or formula use, for example.

Another limitation of our study is that although the volumes of mother's own milk were recorded in detail, we did not have data available on any inter-individual or intra-individual variation in milk composition, and thus estimated the nutrient content of maternal milk based on previous research on lactating mothers of preterm infants.[17] Further, our participants, born in 1978–1985, may not be representative of preterm infants born in high-income settings today: pre- and postnatal care have improved and the rates of IVH, for example, have declined. [50] The mean total energy, carbohydrate, and fat intakes all fell below currently recommended levels (of 110–135kcal, 11.6–13.2g, and 4.8–6.6g/kg/day, respectively) during the first 3-week period, and mean protein intakes were well below current recommendations (3.5–4.5 g/kg/day) for the entire 9-week period. [51] The risk of residual confounding always remains. Finally, a small proportion of infants received nutritional products for which we were unable to trace the exact compositions: for those products, we used the composition data of a closely corresponding product (for example, the same label with composition information available for the previous year). [16]

Conclusions

Our study suggests that the intake of macronutrients during the initial hospitalization period after preterm birth may be linked with benefits for long-term neurodevelopment. However, these intakes, which in our cohort fall below current recommendations, may not act so much as an independent exposure, but rather mediate or reflect the severity of neonatal illness. Future long-term studies in cohorts who have received higher nutrient intakes in line with current guidelines are warranted to either confirm or refute this conclusion.

Supporting information

S1 Table. Executive functioning, attention, and memory in very low birth weight (<1500g) adults.
(PDF)

S2 Table. Intake of carbohydrates, protein, and fats from birth to 3 weeks, 3 to 6 weeks, and 6 to 9 weeks of age, and IQ, VIQ, and PIQ in young adulthood, in individuals born

with very low birth weight (<1500g).^a
(PDF)

S3 Table. Total energy intake and energy intake from human milk from birth to 3 weeks, 3 to 6 weeks, and 6 to 9 weeks of age, and adult IQ, presented separately for those with and without specific neonatal complications and illnesses, in individuals born with very low birth weight (<1500g).
(PDF)

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